This review concerns the AOP publication authored by You Song and Daniel Villeneuve and submitted to Environmental Toxicology & Chemistry. The reviewed materials consisted of a snapshot of the AOP263 "Uncoupling of oxidative phosphorylation leading to growth inhibition," captured from the AOPwiki (https://aopwiki.org/aops/263) along with the accompanying manuscript titled "The adverse outcome pathway for uncoupling of oxidative phosphorylation leading to growth inhibition."

The four reviewers David Dreier, Ksenia Groh, Joel Meyer and Terry Schultz have jointly discussed, prepared, and approved the final review text below.

The reviewers commend the authors for the work carried out to prepare this submission. Uncoupling of oxidative phosphorylation (OXPHOS) is one of several important mechanisms that can lead to mitochondrial dysfunction and toxicity. The MIE "Decrease, Coupling of OXPHOS" is well characterized through multiple studies. The two KEs, "Decrease, Adenosine triphosphate pool" and "Decrease, Cell proliferation" are both at the cell/tissue level of biological organization. The AO "Decrease, Growth" can be assessed at various levels of biological organization, ranging from tissue to organism. Growth inhibition is an accepted regulatory endpoint, addressed, for example, by several OECD test guidelines (TG). In general, the reviewers agree with the AOP organization and description, as well as the assessments made by the authors with respect to the strength of evidence for individual KEs and KERs. However, several aspects, as listed below, might require further consideration and potential revision by the authors.

First, not only the uncoupling of the OXPHOS, but also several other mechanisms could lead to dissipation of the proton-motive force (PMF). Therefore, it may be important to understand whether the observed effects on the PMF are a direct consequence of uncoupling or secondary to another mechanism. In the light of this, we invite the reviewers to consider capturing the "dissipation of the PMF" as a separate KE in this AOP. Inclusion of this event as a separate KE entity could allow intersecting/linking with any future AOPs that would describe mechanisms other than OXPHOS uncoupling that could also lead to PMF dissipation; otherwise, these might remain disconnected.

We notice that the "Background" section in the AOP snapshot is rather short. Perhaps this was intentional, while the "Introduction and background" section of the accompanying manuscript captures more information. However, we feel that also in the manuscript, the readers would certainly benefit from the addition of several important references that are currently missing. In particular, we refer the authors to the following three publications:

- Ebert and Goss 2020: While this paper is purely mechanistic modeling to predict protonophoric uncoupling activity, it has an extensive list of references following the science of respiratory uncoupling. The authors should consider including some of these references in their overview.
- Schultz et al. 2002: This paper presents a comparison of pentachlorophenol (PCP) results with those elicited upon exposure to the model nonpolar narcotic 1-octanol, which revealed marked differences in both growth kinetics and the relative percentages of selected fatty acid methyl esters (FAMEs) in both pellicle and mitochondrial membranes.
- Hawliczek-Ignarski et al. 2017: This paper provides further evidence with regard to PCP's MoA. It is also a good example of how toxicogenomic data could be used to inform AOP development and which kind of testing data could be obtained with toxicogenomic approaches, so the

authors might also consider discussing this particular aspect as well, particularly in the section focused on the toxicity assays relevant for this AOP.

Overall, we do not suggest that the reference list of the presented manuscript needs to approach 100 or even 50 references, but the final reference list should both reflect the history of the subject and identify the key publications along the way. For example, consider also the contributions by Hanstein 1976, McLaughlin and Dilger 1980, and Mitchell 1966. Lastly, we observed that in many cases the references cited in the AOP snapshot are not included in the manuscript. We feel that most of the omitted references would make for a useful addition to the manuscript as well, especially considering that the manuscript might reach a wider readership and therefore needs to be more extensively supported by references, compared to the entry in the AOP wiki.

We also feel that the role and potential significance of the uncoupling proteins (UCPs) may be worth mentioning as well. UCPs are produced and regulated endogenously. Some UCPs play a role in heat generation, while others may play a role in modulating mitochondrial reactive oxygen species production (i.e., mild uncoupling, by decreasing the degree of reduction of ETC complexes, can decrease leakage of electrons to oxygen). See, for example, publication by Brand and Esteves 2005. We invite the authors to consider if the evidence on the effects of UCPs on some downstream events could further support the essentiality of those KEs?

Alternately, we see that down the road, the authors plan to connect uncoupling to mitochondrial ROS production. Inclusion of information on the connection of uncoupling to mtROS production may be more pertinent at that time. At this point, our understanding is that the relationship of mitochondrial uncoupling to mtROS production is that low levels of uncoupling decrease mtROS production, but high levels of uncoupling would eventually cause severe enough loss of mitochondrial homeostasis that mtROS increases. We suspect that this higher-"dose" effect may occur in the context of cytotoxicity, though, where mtROS production may be an effect rather than the proximate cause of mitochondrial dysfunction and cellular toxicity. However, a low-level decrease of mtROS levels could also be deleterious, especially in development, since mtROS signaling is important in developmental patterning and wound healing (Love et al. 2013; Timme-Laragy et al. 2018).

The potential for uncoupling to trigger a compensatory increase in glycolysis should perhaps be mentioned as well. This mechanism has been observed/known for a long time (Weinbach 1957) and it may actually bypass or reduce an apparent decrease in ATP (see for example Bestman et al. 2015), yet still result in an overall decrease in energy availability and growth since glycolysis is less efficient compared to OXPHOS. This important point may also need a separate discussion/mentioning in the section on the overall evidence assessment for this AOP and its KEs and KERs, as well as in the section that discusses alternative tests for this AOP. This is because there is also evidence that you can have compensatory upregulation of other energetic pathways, which will still come at a cost because this also requires energy. With this, you will not be observing an ATP decrease in vivo, although energy limitation would still be occurring, because of the overall less efficient use of available food resources. In vitro, if one would grow cells capable of glycolysis, uncouplers could appear much less toxic under these conditions than if the cells are forced to respire. See, for example, Marroquin et al. 2007.

Page 4 of the AOP snapshot: Table for the Essentiality of the Key Events says that "There are currently no inconsistencies and uncertainties identified by the authors." However, the authors themselves have cited, for example, the case when ATP pool increases upon mild exposure to uncouplers. While the

authors do offer an explanation for why this might be the case, should this not be considered a remaining uncertainty in this pathway, as long as the underlying mechanistic and quantitative relationships have not been characterized in more detail?

Concerning the mentioned “AOP network,” of which the AOP 263 is said to be a “core” part of: We understand that the “AOP Network” is part of AOP-Wiki, but this mention is perceived as a detractor from AOP 263. With regard to this network, it is at the moment not clear, how much of it is still purely theoretical and how much is already listed and well-described with accompanying evidence collected and presented in the AOP wiki. Overall, we feel that, since the manuscript also repeatedly refers to the AOP network in the wiki, then it should also – at least briefly – explain the status of other AOPs belonging to the overall “network” of the AOP 263. Furthermore, the authors need to explain why the presented AOP 263 forms “the core of a larger AOP network” (as compared to the other AOPs in the network – which specific quality or descriptor makes it “the core” of the whole group?) We further observe that the network view contains connections to certain other forms of mitochondrial dysfunction (e.g., CIII and ATP synthase inhibition) but not others (e.g., CI, CII, CIV, redox cycling, Krebs cycle, etc.)—presumably, these will be added in the future? It would be helpful if the authors could comment on this as well.

Looking at the list of the AOPs which include the MIE “Decrease, Coupling of OXPHOS” (on page 9 of the AOP snapshot), one cannot help but wonder whether all 6 (!) AOPs with practically identical names are truly necessary (i.e., all are called “Uncoupling of oxidative phosphorylation leading to growth inhibition”, with numbers 1-6 included in the end). We feel that the authors should provide a more detailed explanation, both in the snapshot and in the manuscript, as to why they find this granular structure necessary and what are the benefits they expect to gain from the proposed formulation of this particular “network” consisting of closely related if not nearly identical pathways.

We point out that event 1771 is also supported by two other studies, i.e., Luz, Lagido, et al. 2016 and Luz, Godebo, et al. 2016, which showed that *in vivo* exposure of *C. elegans* to FCCP caused an increase in oxygen consumption coupled to a decrease in steady-state, *in vivo* ATP levels.

With regard to the “overall assessment” for the KER3 of this AOP (event 1521): this event is supported by in vivo evidence from Bestman et al. 2015. This study has already been cited by the authors in support of the event 1821. However, the findings from this study are worth discussing with regard to event 1521 as well, because it reveals the unsurprising potential for cell- and tissue-specific effects to become larger when they are high-energy-use, potentially leading to teratogenesis in addition to growth inhibition (a mechanism that could perhaps form another AOP?). Therefore, the Bestman et al. 2015 reference should also be cited here as an in vivo example to make a point that there can be large tissue-specific effects and that not every cell type is equally susceptible. The authors should perhaps mention this as a placeholder, in order to ensure that the respective additional AOPs will at some point get constructed as well. These AOPs could also be seen as potential branching points to the AOP in question.

Overall, we do understand that a single AOP cannot be expected to capture all related evidence. However, we also feel that it is quite important to find the right balance between the understandable desire of the authors to be succinct and describe only what’s necessary, but at the same point to avoid a situation when the ‘naïve’ people who would come and read this description would walk away with a feeling that growth inhibition is the only effect that uncouplers might lead to, or that growth inhibition is only caused by uncoupling. Therefore, we feel that more granularity in the descriptions for some KEs, as

well as some more details provided when discussing the supporting evidence, might make for a valuable addition to the manuscript. Our main concern is that we do not want this pathway to be interpreted in isolation and therefore we feel that the potential additional mechanisms, as well as some conflicting evidence, should be properly mentioned and discussed as well. As a suggestion, the authors could consider adding a sentence to their Discussion section in the manuscript, which should explain that, while this particular AOP is focused on a specific, necessarily limited chain of events only, it is also recognized that there are additional outcomes possible. Some of these additional outcomes should then be listed as examples, without being exhaustive of course. The goal of this addition would be that a reader which is new to the field would at least become aware of the associated complexity. This could also open the door to some other AOPs to be developed.

For example, the authors should discuss in more detail the link to teratogenesis as an outcome of growth disruptions manifested in certain organs. Indeed, the occurrence of both the malformed progeny as well as runts (smaller, often retarded siblings within one litter) are both caused by the effects related to developmental toxicity and dependent on cell proliferation capacity. Therefore, both can be seen as hazard endpoints that can be influenced by uncouplers. In the adult (mature) organisms, cell proliferation-related effects could also be particularly relevant for the tissues that maintain active proliferation status throughout life, e.g. gut which is always in a state of active turnover. In contrast, this certainly would not affect the brain, as you typically do not get more neurons. The latter point might again be true in mammals but much less so in fish, where neural tissue proliferation remains a life-long possibility. Some systemic effects (e.g., cardiac toxicity) also partially depend on cell proliferation. Overall, a better characterization of the AO at the organ level should capture some of this discussion. The authors should also add a sentence or two highlighting that there could be related outcomes other than organismal growth. Such discussion helping to relate the AO postulated in this AOP to some of the more traditional in vivo endpoints has the potential to further improve the presented AOP and its usefulness in the context of risk assessment.

Further, on page 3 of the AOP snapshot, in the section on the life stage applicability domain, the authors state that “Classical uncouplers such as 2,4-DNP have been reported to cause weight loss in adult humans […] suggesting that adults are partially in the applicability domain of this AOP.” This statement can and probably should be further strengthened. In fact, 2,4-DNP was sold legally for this purpose (i.e., weight loss), until its legal sale was banned because some people took too much of it and died as a result. This chemical, however, is still available online, and still killing people, unfortunately, see e.g. the report by Baker and Baker 2020. Therefore, human adults are indeed affected and susceptible to the effects of OXPHOS uncouplers.

The susceptibility of adult humans to mitochondrial uncoupling is further supported by what appears to be the first report of a (genetic) mitochondrial disease in people, namely the Luft Disease (Luft et al. 1962). This disease is thought to be caused by mitochondrial uncoupling (unfortunately, the specific gene(s) responsible for this mechanism remain unidentified) and is characterized by hyperthermia, perspiration, and enormous appetite despite low weight. The patient was underweight as a child, despite increased appetite. Again, this example further supports the idea that the uncoupler effects have high human health relevance.

Likely beyond the scope here, but perhaps worth keeping in mind as well: there is currently evidence of mitochondrial uncoupling leading to either increased or decreased neurodegeneration—perhaps related to the non-monotonic effects on mtROS. This could also be another AOP to be developed later.

Overall, we strongly emphasize that for this AOP and the associated effects, the environmental (ecotoxicological) and human health aspects should not be discussed in isolation. Currently, we observe a certain tendency of this AOP to lean more towards discussing the ecotoxicological aspects and applications, while the potential human health effects have been discussed rather cursorily and without going into much detail. We feel that there should be more discussion related not only to environmental health concerns but also to human health concerns, in order to better outline how these findings are specifically related to human health. We do understand that this AOP might have more of an ecotox flavor based on the authors' main expertise, but we do encourage them to expand it according to the directions suggested above.

On the other hand, with regard to ecotoxicological applications of this AOP, we were also somewhat surprised to observe that, while the authors do talk about growth on the tissue, organ and organismal level, they have not outlined any potential connection to population-level outcomes. At the same time, this AOP does place a lot of emphasis on its ecotoxicological relevance, as we have just discussed above. Therefore, we consider that it would be valuable if authors also compiled the evidence available with regard to potential population-level effects as well.

Further, with regard to environmental relevance, the authors should please elaborate on the significance of a lower acute-to-chronic ratio (ACR) for uncouplers (mentioned at line 255 in the manuscript). An important point to make here could be to explain, what the potential consequences of that could be.

With regard to the sex applicability domain of this AOP, we encourage the authors to consider including a study looking at PCP-caused decreased growth in rats (Schwetz et al. 1978), as there are also some sex-specific effects described in this paper.

The statement on Page 3 of the AOP snapshot, "The chemical applicability domain of the AOP mainly includes weak acids, such as …." is accurate, but perhaps it would also be helpful to explain why this is the case. That is, describe that uncouplers typically have properties as both weak acids and hydrophobic substances. As weak acids, they are capable of gaining and losing an electron. As hydrophobic substances, they are capable of distributing a negative charge over a number of atoms (often by π-orbitals which delocalize a proton's charge when it attaches to the molecule), so that they can diffuse back and forth across the IMM in either the charged or uncharged state, thus moving protons back across the concentration gradient generated by the ETC. A more detailed discussion of these mechanisms could be useful for any future analyses by scientists who might be interested to apply physicochemical property analysis to discovery of uncouplers.

We also observe that the chemical applicability domain of this AOP, which appears to be mainly focused on weak acids, might be unnecessarily narrow. It is not completely clear to us if hydrophobic ion or SH-reactive types of uncouplers have been considered/included as well. It would be helpful if the authors could clarify this point.

We further note that historically (e.g., in the cases of AOPs on skin sensitization or AOPs for estrogen-mimicking substances), AOPs have always included some discussion of applicability domains. However, one also needs experimental data on classic uncouplers within themselves to suggest an applicability domain. For example, 2,4-dinitro-, pentachloro- and 3,5-dichloro-phenol suggest the phenolic weak acid domain. But not all nitro/chlorophenols are uncouplers of sufficient strength to decrease growth before death occurs. In our view, one of the seminal functions of an AOP could be guiding direct testing to define the boundaries of its applicability domains.

With regard to the section on alternative assays: It is noted that three out of four KEs in this AOP can be measured using high-throughput in vitro assays. We were wondering if data from these assays could also be used as empirical support for the key event relationships? We suggest that, for assays that capture multiple key events, this information could be added to the concordance table, i.e. Table S1 in the supplementary material, as these would constitute useful additional lines of evidence for the key event relationships. For further information on the multiplexed assays, see Shah et al. 2016.

We also observe that a more detailed description of assays that could be used and would be important for the endpoints associated with the MIE and KEs in the outlined AOP is very critical, because this will go through the OECD. For applications there, it is not enough to just have a pathway, but you also need to have the assays with which it can be measured. Consequently, an AOP could be stuck at OECD if there are no good ways to measure an important KE. Therefore, better outlining these assays would be a critical point to move forward with this AOP.

AOP snapshot, page 2, the section on stressors: “moderate” evidence is given for pentachlorophenol while “high” is mentioned for all other listed chemicals. We were not able to locate a clear explanation for why the evidence for PCP is only moderate. In this regard, we also invite the authors to consider PCP-related evidence from studies by Schultz et al. 2002 and Hawliczek-Ignarski et al. 2017.

Further with regard to regulatory significance and potential applications of this AOP: We observe that the AO “Decrease, Growth” refers to growth inhibition, which is accepted as a regulatory endpoint in many countries (though not all) and has been addressed by several OECD test guidelines (TG). In a regulatory context, effects on growth can be measured with parameters such as length, wet or dry weight, or as a rate over time (as is common in algae). The authors do list some of these TGs in the section “Regulatory significance of the AO.” This section could be further expanded to also include guidelines for chronic toxicity testing in fish (TG 210) and birds (TG 206), thereby improving the applicability of this AOP as a framework for animal alternative approaches. In addition, the authors may consider adding a short discussion of the main differences in legislative mandates that some countries have with regard to growth as a regulatory endpoint. Overall, we feel that the discussion in this section should be expanded to explain how this AOP relates to the real world in terms of regulatory practice. For example, the authors could provide concrete examples linking different organisms to the listed TGs, as this would allow different regulatory bodies from across the world to better relate to this particular AOP.

While the ‘consideration for potential application of the AOP’ is optional in the AOP-Wiki, we deem it highly critical to publication in ET&C. We suggest that each of the presented considerations should be discussed in more detail in the manuscript. That is, not just listing with one sentence, but elaborating and presenting additional evidence and further considerations, as well as concrete examples or potential case studies for each point, where available.

With regard to the presented considerations themselves, we agree with most of them. One exception, however, is the fourth consideration, stating that the AOP is "highly generalized and has wide biological and stressor applicability domains, making it a central hub for many other AOPs." We understand that this consideration may stem from the assumptions and expectations associated with the previously mentioned "AOP network." However, we feel that this is rather speculative, as no specific proofs have been provided so far and we are not completely convinced of the utility or applications of this particular network (see also above for additional considerations regarding the "network" aspect).

We also suggest that the authors try to better illustrate the connections and interdependencies between the points raised. For example, linking considerations 3 and 5 should be emphasized, as this seems to be the classic way that the AOP provides the mechanistic/mode of action plausibility/probability needed to identify the most endpoint relevant and key event-related test systems, which, when used, could help define the boundaries of 2D structure applicability domains and establish structure alerts for predicting potency by read-across or QSAR.

One final consideration that came to our mind: can it be identified, which KE (or an MIE) represents the rate-limiting step in this AOP? This thinking was triggered by the estrogen-mimic AOP where ER-binding is the rate-determining step and fish liver vitellogenesis assay confirms this. The male-to-female gonadal conversion, feminization of male fish, and reproductive impairment are all downstream events that added weights-of-evidence to that AOP, but data for these events are not needed to make a regulatory decision. However, perhaps these considerations are going a step too far?

Thank you for providing the Tox21 data in the supplementary table S2. The assay documentation indicates this assay measures the mitochondrial membrane potential, and ATP content is used to measure cell viability in the assay (Attene-Ramos et al. 2015). If possible, it would be useful to include the cell viability data to discern specific effects on the mitochondrial membrane potential from general cytotoxicity. Providing both measures would give a clearer context for interpreting these data. Additionally, it is important to note this assay does not measure uncoupling directly, but rather, quantifies changes in the mitochondrial membrane potential as a potential consequence of uncoupling. Indeed, this information has been used to prioritize substances for additional mechanistic studies to identify uncouplers (Xia et al. 2018). It may also be important to note other high-throughput screening assays, such as respirometric screening assays, that can be used to identify specific mechanisms of action, including uncoupling (Hallinger et al. 2020).

<u>Minor comments</u>

In the sentence "A number of chemicals can bind to the inner mitochondrial membrane" (in the Background section), "bind to" should be replaced with "partition into" (because the "binding" work is more associated with events like binding to a receptor, not dissolving into a membrane).

Line 109 in the manuscript: "The MIE, "decrease, uncoupling of OXPHOS", is a lumped term representative of…": replace "uncoupling" by "coupling" in the MIE name.

Line 203 in the manuscript: insert "to" before "this"

Line 218: "… non-vertebrate models" – please specify, such as?

Line 233: "… relationships between uncoupling of OXPHOS and ATP synthesis …" However, what is critical to the final ATP pool is not only the ATP synthesis, but also ATP consumption processes – are there also models taking these into account?

Line 246: the authors might also consider the model developed for predicting fish growth based on cell proliferation, as described in Stadnicka-Michalak et al. 2015.

Page 3 of the AOP snapshot: at the top of the page in the tabular section on "Life Stage Applicability", the evidence for "Juvenile" is listed as "Not Specified." However, later on the same page, in the free-text section, juveniles are listed as known applicability domain, similarly as in several other pages in later sections (for example, page 10, evidence for Juvenile is given as "high"). Perhaps the first instance stating "unspecified" represents a typo and should be changed?

Page 10, in the section "Evidence for Perturbation by Stressor", in the first bullet point, insert "share" before "several", i.e. "These protonophores share several common…"

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